

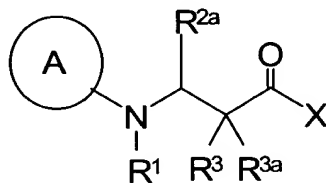
### REMARKS

At the outset, all of the amendments made herein have been made solely to expedite prosecution of claims to what is believed to be allowable subject matter. Applicants specifically reserve the right to file one or more continuation/divisional applications to present claims directed to the canceled subject matter. It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks.

#### Amendments

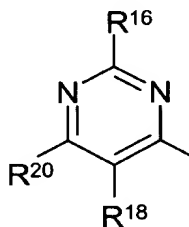
The original pending claims have been canceled without prejudice.

New Claims 27 to 52 have been added. The newly presented claims are directed to compounds which the Examiner has kindly pointed out avoid an improper Markush group rejection. That is Claims 27 to 52 are directed to compounds of Formula I:



(I)

wherein Ring A has been limited to rings of the following formula:



Support for these amendments can be found in the originally filed Claims 1 to 26.

In so far as the newly presented claims represent a similar, but narrower claim scope as compared to the originally presented claims, the rejections raised in the Office Action are addressed as they relate to Claims 27-52.

### Improper Markush Rejection

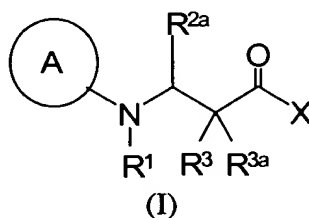
Turning now to the Office Action, Claims 1-26 were rejected as purportedly "drawn to an improper Markush group, that is, the claims lack unity of invention." *See Office Action, Pages 2-3*. According to the Examiner, "ring A is formed in such a way that it keeps changing the core of the compound that determines the classification. ... the structural formula I does not have a significant structural feature that is shared by all of its alternatives which is inventive." *See Office Action, Pages 2-3*. Contrary to this, Applicants submit that parent Claim 1 and Claims 2 to 26 directly or indirectly dependent thereon, do in fact define a proper Markush group.

Whether a Markush grouping is proper is decided on a case-by-case basis. *In re Harnisch*, 631 F.2d 716, 722 (C.C.P.A. 1980); *In re Jones*, 74 U.S.P.Q. 149, 151 (C.C.P.A. 1947). A Markush grouping is proper where the substances grouped have a community of chemical and physical characteristics which justify their inclusion in a common group, and such inclusion is not repugnant to the principles of scientific classification. *In re Schechter*, 205 F.2d 185, 189 (C.C.P.A. 1953).

In determining the propriety of a Markush grouping, compounds are to be considered as a whole, and should not be broken down into elements or other compounds. *Jones*, 74 U.S.P.Q. at 151. Moreover, any differences among members of the group must be weighed against similarities. *Id.*

#### **1. The Compounds Must Be Considered As A Whole**

In the instant case, there is one formula, Formula I, which figures predominantly in the Markush rejection:

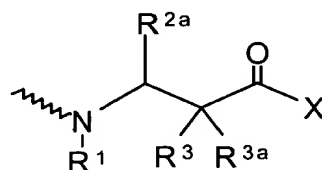


In rejecting the Claims as purportedly drawn to an improper Markush group, the Examiner states, "ring A is formed in such a way that it keeps changing the core of the compound

that determines the classification." *See Office Action, Pages 2-3.* The Examiner's position does not consider the N-substituted  $\beta$ -amino acids *as a whole*, but instead immediately focuses on the terminal portion of each formula. The Examiner's emphasis on this portion, and not the whole compound, runs contrary to a proper Markush analysis. *See Jones*, 74 U.S.P.Q. at 151.

**2. The Compounds Possess A Community Of Chemical And Physical Characteristics Which Justify Their Inclusion In A Common Group**

"From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae ... are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to *identify* what is being patented ... the *thing* that is patented is not the formula but the compound identified by it." *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). The N-substituted  $\beta$ -amino acids identified by graphic Formula I share a community of chemical characteristics, including the fact that these compounds bind to VLA-4. Therefore, these compounds are useful in the prevention and/or treatment of diseases mediated by VLA-4. *See Specification, Page 88 Line 15 to Page 89, Line 17.* In addition, these compounds share a significant common structural element in that they all contain a common N-substituted  $\beta$ -amino acid group of the formula:



In accordance with Applicants' invention, Applicants' N-substituted  $\beta$ -amino acid compounds possess the common activities of binding VLA-4 and accordingly share a common significant utility. Accordingly, their inclusion in a common group is justified, and such inclusion is not repugnant to the principles of scientific classification. *See Schechter*, 205 F.2d at 189.

### 3. Summary

Based on the foregoing, it is evident that when the N-acetyl substituted amino acid amides of Formula I are considered as a whole, they have a community of chemical and physical characteristics which justify their inclusion in a common group, and such inclusion is not repugnant to the principles of scientific classification. Nevertheless, in order to expedite prosecution of what is submitted to be patentable subject matter, Applicants have replaced Claims 1 - 26 with Claims 27 to 52 which have been limited in accordance with the Examiner's suggestions for overcoming the rejection and clearly define a proper Markush group. Accordingly, it is submitted this rejection has been obviated.

#### Rejection Under 35 U.S.C. §112, second paragraph

Originally presented Claims 1-26 (now Claims 27-52) have been rejected for being indefinite, for various reasons discussed below.

More specifically the Office Action regarded the terms substituted alkyl, substituted alkenyl, etc be indefinite because one can not tell which substituents are intended and which are not. Applicants disagree with this assertion because each of these terms is clearly defined in the specification. Nevertheless Claim 27 (which corresponds to originally presented Claim 1) incorporate the lists of specific substituents from these definitions to more clearly point out which substituent are intended. Accordingly this rejection has been obviated and its withdrawal is requested.

The Office Action regarded the terms heteroaryl and heterocyclic to be indefinite because one can not tell which heteroatoms are present and how many are intended. Applicants disagree with this assertion because each of these terms is clearly defined in the specification. Nevertheless Claim 27 (which corresponds to originally presented Claim 1) has been amended to incorporate the lists of specific heteroaryl and heterocyclic groups from the definitions to more clearly point out that which Applicants consider to be their invention. Accordingly this rejection has been obviated and its withdrawal is requested.

The last phrase in Claim 27 (which corresponds to originally presented Claim 1) has been amended to read in the alternative, as requested by the examiner. For

consistency, similar phrases found in Claims 34, 42 and 46 (which correspond to originally presented Claims 10, 18 and 21) have been amended in the same way. Accordingly this rejection has been obviated and its withdrawal is requested.

The Office Action has asserted that it is unclear which compounds of Formula I have a binding affinity to VLA-4 of 15  $\mu$ m or less. Applicants traverse these rejections and note that the specification very clearly describes the methods required to test a compound for its ability to bind VLA-4. This can be found in Example A titled "*In vitro* Assay for Determining Binding of Candidate Compounds to VLA-4" on page 102 in Applicants' specification. Applicants submit that this rejection was made in error and request that it be withdrawn.

The Office Action also alleges that the term "about" is unclear. Applicants' traverse for the following reason. As is pointed out in the MPEP 2173.05(b), the term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was held to be clear, but flexible. Ex parte Eastwood, 163 USPQ 316 (Bd. App. 1968). Similarly, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite because infringement could clearly be assessed through the use of a stopwatch. The court did hold that claims reciting "at least about" were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). As there is no prior art with close or similar limitations on the activity of VLA-4 binding compounds cited against the present invention in this Office Action, Applicants submit that this rejection is improper and request that it be withdrawn.

In addition the Office Action rejects Claims 48 and 50 (which correspond to originally submitted Claim 24) because it is unclear which diseases are mediated by VLA-4 and which are not. Applicants traverse this rejection. There are a number of diseases and conditions which are well-known in the art as being mediated, at least in part, by VLA-4.

Reviews indicating the state of the art have been incorporated by reference on page 3 lines 29-30 the specification. Applicants submit that this rejection was made in error and request that it be withdrawn.

Finally the Office Action objected to Claim 52 (which corresponds to originally submitted Claim 26), because the term "biological sample" is unclear. Claim 52 is drawn to biological samples which are derived from a patient in the form of a blood or plasma sample to more clearly point out what is intended by the term "biological sample". Accordingly this rejection has been obviated and its withdrawal is requested.

In summary, Applicants maintain that the outstanding rejections have either been made in error or have been obviated. From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions relating to this Response, or the application in general, it would be greatly appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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